510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k122187

B. Purpose for Submission:

Premarket notification in support of clearance of Bio-Rad **VRE***Select*™ for the qualitative detection of vancomycin-resistant *Enterococcus faecium* and *E. faecalis* in stool samples.

C. Measurand:

Vancomycin resistant *E. faecium* and *E. faecalis*

D. Type of Test:

Detection of vancomycin resistant *Enterococcus faecium* and *Enterococcus faecalis* using a selective and differential chromogenic medium.

E. Applicant:

Bio-Rad

F. Proprietary and Established Names:

VRE*Select*™ Culture Medium

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1700

2. Classification:

   Class II

3. Product code:

   JSO Culture media, Antimicrobial susceptibility test, excluding Mueller Hinton Agar

4. Panel:

   83; Microbiology

H. Intended Use:

1. Intended use:

   VRE*Select*™ is a selective and differential chromogenic medium, containing 8 µg/mL of vancomycin, for the qualitative detection of gastrointestinal colonization of vancomycin-resistant *Enterococcus faecium* (VREfm) and vancomycin-resistant *Enterococcus faecalis* (VREfs) and to aid in the prevention and control of vancomycin-resistant *Enterococcus* (VRE) in healthcare settings. The test is performed on rectal swabs, or fecal specimens from patients to be screened for VRE colonization. **VRE***Select*™ is not intended to diagnose VRE infection nor to guide or monitor treatment of infection. Results can be interpreted after 24 to 28 hours incubation. Subculture to non-selective media (e.g., trypticase soy agar with 5% sheep blood) is needed for further identification, susceptibility testing and epidemiological typing.

2. Indications for use:

   VRE*Select*™ is a selective and differential chromogenic medium, containing 8 µg/mL of vancomycin, for the qualitative detection of gastrointestinal colonization of vancomycin-resistant *Enterococcus faecium* (VREfm) and vancomycin-resistant *Enterococcus faecalis* (VREfs) and to aid in the prevention and control of vancomycin-resistant *Enterococcus* (VRE) in healthcare settings. The test is performed on rectal swab, or fecal specimens from patients to be screened for VRE colonization. **VRE***Select*™ is not intended to diagnose VRE infection nor to guide or monitor treatment of infection. Results can be interpreted after 24 to 28 hours incubation. Subculture to non-selective media (e.g., trypticase soy agar with 5% sheep blood) is needed for further identification, susceptibility testing and epidemiological typing.

3. Special conditions for use statement:

   Prescription use.

   The performance of **VRE***Select*™ has not been evaluated with vancomycin resistant strains of *Staphylococcus aureus.*

   After 24 to 28 hours incubation pink colonies can be reported as vancomycin-resistant *Enterococcus faecium*. Blue colonies should be confirmed by a direct catalase test and, if negative, by vancomycin susceptibility testing.

4. Special instrument requirements:

   Not Applicable.

I. Device Description:

VRE*Select*™ is a selective medium for the detection of vancomycin-resistant *Enterococcus* (VRE). The selectivity of this medium is based on the presence of an antifungal/antibiotic mixture that inhibits the growth of most yeast, Gram negative and Gram positive bacteria, with the exception of VRE. Vancomycin-resistant *E. faecium* will appear as pink colonies on the agar medium. Blue colonies on the agar medium, suggestive of vancomycin-resistant *E. faecalis* should be confirmed by catalase and antimicrobial susceptibility testing.

J. Substantial Equivalence Information:

1. Predicate device name:

   Remel Spectra VRE Chromogenic Media

   Remel Bile Esculin Azide Agar w/ 6µg/mL Vancomycin

2. Predicate K number:

   K092819

   K972359

3. Comparison with predicate:

Similarities			
Item	Device	Predicate K092819	Predicate K972359
Intended Use	**VRE***Select* ™ is a selective and differential chromogenic medium, containing 8µg/mL of Vancomycin, for the qualitative detection of gastrointestinal colonization of vancomycin-resistant *Enterococcus faecium* (VREfm) and vancomycin-resistant *Enterococcus faecalis* (VREfs) and to aid in the prevention and control of vancomycin-resistant Enterococcus (VRE) in healthcare settings. The test is performed on rectal swabs or fecal specimens from patients to be screened for VRE colonization. **VRE***Select* ™ is not intended to diagnose VRE infection nor to guide or monitor treatment of infection. Results can be interpreted after 24 to 28 hours incubation. Subculture to non-selective media (e.g., trypticase soy agar with 5% sheep blood) is needed for susceptibility testing and epidemiological typing.	Remel Spectra VRE is a selective and differential chromogenic medium, containing 6µg/mL of Vancomycin, intended for use in the qualitative detection of gastrointestinal colonization with vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE) to aid in the prevention and control of VRE in healthcare settings. The test is performed with a rectal swab and fecal specimens from patients to screen for VRE colonization. Spectra VRE is not intended to diagnose VRE infection or to guide or monitor treatment for infections. Subculture to non-selective media (e.g. Tryptic Soy Agar with 5% sheep blood) is needed for further identification, susceptibility testing, and epidemiological typing.	Remel Bile Esculin Azide Agar w/ 6µg/mL vancomycin is a plated medium recommended for use in qualitative procedures as a selective and differential medium for the primary isolation of vancomycin-resistant enterococci from surveillance cultures. This product is not intended for use as [a] method of antimicrobial susceptibility testing. Confirmation of resistance by an approved method is recommended as some organisms on initial isolation may overcome the inhibitory effects of the medium.
Methodology	Enzymatic	Enzymatic	Enzymatic
Interpretation	Manual, Visual	Manual, Visual	Manual, Visual
Sample Type	Stool/fecal specimens	Rectal Swabs or Fecal Specimens	Rectal Swabs or Fecal Specimens
Differences			
Inoculation	Direct or Indirect	Direct Specimen	Direct Specimen

K. Standard/Guidance Document referenced (if applicable):

Not Applicable.

L. Test Principle:

VRE*Select* ™ is a selective medium for the detection of vancomycin-resistant *Enterococcus* (VRE). The selectivity of this medium is based on the presence of an antifungal/antibiotic mixture that inhibits the growth of most yeasts, Gram negative and Gram positive bacteria, with the exception of VRE.

Detection is based on the cleavage of chromogenic substrates by specific enzymes of *Enterococcus faecium* which produces pink colonies and *Enterococcus faecalis* which produces blue colonies.

Enterococcus gallinarum and *Enterococcus casseliflavus* are intrinsically resistant to vancomycin and may grow on the **VRE***Select*™ medium as colorless or white colonies because they do not metabolize the chromogenic substrates. Vancomycin-susceptible enterococci are inhibited.

After 24 to 28 hours incubation pink colonies can be reported as vancomycin-resistant *E. faecium* and blue colonies should be confirmed by a catalase test and susceptibility testing.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

      Reproducibility was demonstrated at three sites using a blinded panel of six ATCC reference strains including two vancomycin-resistant *E. faecalis* strains, three vancomycin-resistant *E. faecium* strains and one strain of vancomycin-susceptible *E. faecalis.* At each site, three technicians tested the panel on three lots of the **VRE***Select*™ each day, for three days. The strains produced the expected results with the **VRE***Select*™ 100% of the time both at 24 and 28 hours.

   b. *Linearity/assay reportable range:*

      Not Applicable.

   c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

      The following recommended quality control (QC) organisms were used: *E. faecium* (*van*A) ATCC 700221 and *E. faecalis* (*van*B) ATCC 51299 as positive controls, and *E. faecalis* ATCC 29212 as negative control. Quality control was performed on each day of testing by preparing a 0.5 McFarland suspension of each QC strain then diluting is 1:10 and transferring 10 µL of

this suspension to the **VRE**Select™ agar surface streaking for isolation. Quality control data was compiled across all three sites and overall QC results were acceptable.

QC Data Summary

QC Strain	Expected Results after 24- 28 hours at 35- 37°C
Enterococcus faecalis ATCC 51299	Growth- small blue colonies
Enterococcus faecium ATCC 700221	Growth- small pink colonies
Enterococcus faecalis ATCC 29212	No growth

d. Detection limit:

The minimum concentration of VRE reliably detected by **VRE***Select* ™ is 10^3 CFU/mL. Details of the recovery study are found in Section f below.

e. Analytical specificity:

Cross-reactivity Study

A Cross-reactivity study was performed using at total of 119 strains of Gram negative rods, Gram positive cocci and yeast. No cross-reactivity was observed with any of the organisms tested and no variation was seen between the 24 and 28 hour incubation time.

Interference Study

The following substances were evaluated at physiologically or biologically relevant concentrations for potential interference with the performance of the **VRE***Select*™ medium:

- Dulcolax, Adult Glycerin Suppositories, Vaseline, Preparation H, Original Boudreaux's Butt Paste, Tuck's Medicated Cooling Pads, Pepto-Bismol, Miconazole cream, Nonoxynol-9 (spermicide), KY Jelly, and Pepcid AC Max strength.
- Blood and Mucins
- Three commonly used transport media – Amies without charcoal, Cary Blair and LQ Stuart

The interfering substances tested caused no significant differences between the number of colonies observed on the control plates and the number of colonies observed on the **VRE***Select*™ plates. The only exceptions were Tuck's Medicated Cooling Pads and Miconazole cream. Regarding Tuck's Medicated Pads, no pink coloration was observed after 24 hours on the **VRE***Select*™ plates that had been inoculated with vancomycin-resistant *E. faecium* (ATCC 700221). Regarding Miconazole cream, an inhibitory effect on the growth of *Enterococcus* colonies on the **VRE***Select*™ plates was

observed. Blood and mucin (3% to 5%) caused delayed colonial growth of one strain of vancomycin-resistant *E. faecalis* (ATCC 51299) tested. The growth of the same strain of vancomycin-resistant *E. faecalis* was inhibited at blood and mucin concentrations of 30% to 50%.

Mixed Infection Study

A mixed infection study was conducted to demonstrate that high levels ($1X10^7$ CFU/mL or higher) of *E. gallinarum* and/or *E. casseliflavus* will not suppress the growth of vancomycin-resistant *E. faecium* or *E. faecalis*. The results of the study revealed *E. faecium* or *E. faecalis* are still detected on the **VRE***Select* ™ medium in the presence of high levels of *E. casseliflavus* and *E. gallinarum*.

f. Analytical Sensitivity

Recovery Study
The minimum concentration of VRE reliably detected by **VRE***Select* ™ is 10^3 CFU/mL.

To determine the percent recovery for the **VRE***Select* ™ media a panel of eighteen (18) vancomycin-resistant Enterococci (VRE)– (8) strains of vancomycin-resistant *E. faecium* and (10) strains of vancomycin-resistant *E. faecalis* – were tested at varying dilutions. A 0.5 McFarland suspension of each strain was prepared. A series of 10-fold serial dilutions in saline were carried out and inoculated onto three lots of **VRE***Select* ™ plates and one lot of Blood Agar plates. The plates were incubated at 35-37°C ambient air and read at 24 and 28 hours. The color and number of colonies were recorded. The Blood Agar plates were used to confirm the inoculum concentration at each dilution. Data confirm that the minimum concentration of VRE reliably detected by **VRE***Select* ™ is 10^3 CFU/mL.

g. Assay cut-off:

Not Applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The performance of the **VRE***Select*™ agar medium was evaluated at three laboratory sites. A total of 946 fecal samples were evaluated. Fecal samples were inoculated using the indirect inoculation method where approximately 0.5 g of stool is placed in 1 mL of saline, then mixed by vortexing. Using a swab or a disposable loop, approximately 10-50 µl is transferred onto the **VRE***Select*™ agar medium and the Bile Esculin Azide Agar with 6µg/ml of

Vancomycin (BEAV). The BEAV plates were observed for growth at 24 and 48 hours. The **VRE***Select*™ plates were observed at 24 and 28 hours. Colonies with blue or pink pigment (**VRE***Select*™) or brown to black pigment diffusing into the medium (BEAV), were identified by a combination of conventional reference methods to include Gram stain, catalase, PYR, VITEK 2 identification, and vancomycin MIC E-Test.

Percent agreement of the **VRE***Select*™ compared to BEAV and conventional methods is presented in Table 1. Specimens that were positive on the **VRE**Select (i.e. grew pink or blue colonies between 24 and 28 hours incubation) were compared to specimens that were confirmed positive based on growth and pigment on BEAV combined with Gram stain, catalase test, PYR test, biochemical identification, and E-test MIC)

		Table 1. BEAV +Confirmation	
		% Positive Agreement	% Negative Agreement
VRE*Select*™	24 hrs	96% (182/189, [CI. 0.92, 0.98])	96% (727/757, [CI. 0.94, 0.97])
	28 hrs	98% (186/189, [CI. 0.95, 0.99])	95% (721/757, [CI. 0.93, 0.96])*

* Thirty-three (33) of the 36 specimens that were BEAV plus Confirmation negative and that grew pink and/or blue colonies on **VRE***Select*™ media, after subculture to blood agar plates (BAPs), were confirmed to be vancomycin resistant *E. faecium* and/or *E. faecalis* by biochemical identification and vancomycin E-Test. Three (3) specimens that were BEAV plus Confirmation negative and that grew pink and/or blue colonies on **VRE***Select*™ media, after subculture to blood agar plates (BAPs), were not confirmed biochemical identification and vancomycin E-Test to be *E. faecium* and/or *E. faecalis* and represent false positive results.

Performance data for the **VRE***Select*™ agar medium compared to biochemical identification, for both isolates of *E. faecalis* (VREfs) and *E.faecium* (VREfm) is presented in Table 2.

	Table 2. Vitek 2 Biochemical Identification		
	% Positive Agreement		% Negative Agreement
VREfm			
VRE*Select*™ @ 24 hours	94% (171/181, [CI. 0.90, 0.97])		97% (740/765, [CI. 0.95, 0.98])
VRE*Select*™ @ 28 hours	97% (175/181, [CI. 0.93, 0.99])		96% (734/765, [CI. 0.94, 0.97])
VREfs			
VRE*Select*™ @ 24 hours	94% (15/16, [CI. 0.70, 0.99])		98% (910/930, [CI. 0.97, 0.99])
VRE*Select*™ @ 28 hours	94% (15/16, [CI. 0.70, 0.99])		98% (909/930, [CI. 0.97, 0.99])

Performance data for the **VRE***Select*™ agar medium compared to the vancomycin MIC E-test, for both isolates of *E. faecalis* and *E. faecium* are presented in Table 3. Specimens that were identified in the reference arm of the study as vancomycin-resistant and identified as *E. faecium* or *E. faecalis* by biochemical identification and grew pink or blue colonies on **VRE***Select*™ were considered in positive agreement.

	Table 3. Vancomycin Resistance (E-Test)		
	% Positive Agreement		% Negative Agreement
VREfm			
VRE*Select*™ @ 24 hours	96% (171/178, [CI. 0.92, 0.98])		97% (743/768, [CI. 0.95, 0.98])
VRE*Select*™ @ 28 hours	98% (175/178, [CI. 0.95, 0.99])		96% (737/768, [CI. 0.94, 0.97])
VREfs			
VRE*Select*™ @ 24 hours	100% (12/12, [CI. 0.82, 1.00])		98% (911/934, [CI. 0.96, 0.99])*
VRE*Select*™ @ 28 hours	100% (12/12, [CI. 0.82, 1.00])		97% (910/934,[CI. 0.96, 0.98])

b. Matrix comparison:

Not Applicable.

3. Clinical studies:

a. Clinical Sensitivity:

Not Applicable.

b. Clinical specificity:

Not Applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable.

4. Clinical cut-off:

Not Applicable.

5. Expected values/Reference range:

   Vancomycin resistant *E. faecalis* presents as blue color colonies which should undergo catalase and susceptibility testing.

   Vancomycin resistant *E. faecium* presents as pink color colonies.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence evaluation.